

What is claimed is:

1. A method of predicting the survival outcome of an individual suffering from severe congestive heart failure, said method comprising:

a) determining as the first marker a level of Big ET-1 (1-38) or its immunologically detectable fragments in the individual; and

b) determining as the second marker a level of proANP or its immunologically detectable fragments, proBNP or its immunologically detectable fragments or ET-1 or its immunologically detectable fragments in the individual, wherein Big ET-1 or its immunologically detectable fragments does not include ET-1 or its immunologically detectable fragments;

or

a') determining as the first marker a level of N-ProBNP or its immunologically detectable fragments in the individual; and

b') determining as the second marker a level of BNP or its immunologically detectable fragments in the individual;

comparing the level of the first and second markers to cut-off levels of these markers in age matched normal individuals, said cut-off levels distinguishing between high and low survival rate due to cardiovascular cause,

wherein the likelihood of death from cardiovascular cause is greatest when said individual has first and second marker levels that are both greater than their cutoff levels, the likelihood of death from cardiovascular cause is least when said individual has first and second marker levels that are both less than their cutoff levels, and the likelihood of death from cardiovascular cause is intermediate when said individual has one marker level greater than its cutoff level and the other marker level less than its cutoff level.

2. The method of claim 1 wherein said first marker is Big ET-1 (1-38) or its immunologically detectable fragments and said cutoff level is about 2.4-5.0 fold the normal level, and said second marker is proANP or its immunologically detectable fragments and said cutoff level is about 3.3-12 fold the normal level.

3. The method of claim 2, wherein said first marker is Big ET-1.

4. The method of claim 3, wherein said cutoff level of Big ET-1 (1-38) is about 3.5-5.0 fold the normal level for Big ET-1 (1-38).

5. The method of claim 3, wherein said cutoff level of Big ET-1 (1-38) is about 4.1 fold the normal level for Big ET-1 (1-38).
6. The method of claim 2, wherein said first marker is Big ET-1 (22-38).
7. The method of claim 6, wherein said cutoff level of Big ET-1 (22-38) is about 2.4-2.6 fold the normal level for Big ET-1 (22-38).
8. The method of claim 6, wherein said cutoff level of Big ET-1 (22-38) is about 2.5 fold the normal level for Big ET-1 (22-38).
9. The method of claim 2, wherein said second marker is proANP.
10. The method of claim 2, wherein said second marker is N-proANP (1-98) or its immunologically detectable fragments.
11. The method of claim 10, wherein said cutoff level of N-proANP (1-98) or its immunologically detectable fragments is about 3.3-4.4 fold the normal level for N-proANP (1-98).
12. The method of claim 10, wherein said cutoff level of N-proANP (1-98) or its immunologically detectable fragments is about 3.8 fold the normal level for N-proANP (1-98).
13. The method of claim 10, wherein said second marker is N-proANP (1-25).
14. The method of claim 13, wherein said cutoff level of N-proANP (1-25) is about 9.5-12 fold the normal level for N-proANP (1-25).
15. The method of claim 13, wherein said cutoff level of N-proANP (1-25) is about 10.7 fold the normal level for N-proANP (1-25).
16. The method of claim 10, wherein said N-proANP is N-proANP (68-98).
17. The method of claim 16, wherein said cutoff level of N-proANP (68-98) is about 8.5-10.8 fold the normal level for N-proANP (68-98).
18. The method of claim 16, wherein said cutoff level of N-proANP (68-98) is about 9.6 fold the normal level for N-proANP (68-98).
19. The method of claim 2, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proANP or its immunologically detectable fragments are both below the cutoff level, the individual's 50% survival for death from cardiovascular cause is at least about 45 months.

20. The method of claim 2, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proANP or its immunologically detectable fragments are both below the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is at least about 75 months.

21. The method of claim 12, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proANP or its immunologically detectable fragments are both below the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is at least 91 months.

22. The method of claim 2, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proANP or its immunologically detectable fragments are both higher than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 5.5 months.

23. The method of claim 1, wherein severe congestive heart cause is defined as NYHA class III-IV.

24. The method of claim 1 wherein said first marker is Big ET-1 (1-38) or its immunologically detectable fragments, and said cutoff level is about 2.4-5.0 fold the normal level and said second marker is proBNP or its immunologically detectable fragments and said cutoff level is about 4.7-89 fold the normal level.

25. The method of claim 24, wherein said first marker is Big ET-1.

26. The method of claim 25, wherein said cutoff level of Big ET-1 (1-38) is about 3.5-5.0 fold the normal level for Big ET-1 (1-38).

27. The method of claim 25, wherein said cutoff level of Big ET-1 (1-38) is about 4.1 fold the normal level for Big ET-1 (1-38).

28. The method of claim 24, wherein said first marker is Big ET-1 (22-38).

29. The method of claim 28, wherein said cutoff level of Big ET-1 (22-38) is about 2.4-2.6 fold the normal level for Big ET-1 (22-38).

30. The method of claim 28, wherein said cutoff level of Big ET-1 (22-38) is about 2.5 fold the normal level for Big ET-1 (22-38).

31. The method of claim 24, wherein said second marker is N-proBNP or its immunologically detectable fragments and said cutoff level of N-proBNP or its

immunologically detectable fragments is about 4.7-6.8 fold the normal level for N-proBNP or its immunologically detectable fragments.

32. The method of claim 24, wherein said first marker is N-proBNP or its immunologically detectable fragments and said cutoff level of N-proBNP or its immunologically detectable fragments is about 5.7 fold the normal level for N-proBNP or its immunologically detectable fragments.

33. The method of claim 24, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proBNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is at least about 31-61 months.

34. The method of claim 24, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and proBNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 4.5-7.5 months.

35. The method of claim 31, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and N-proBNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 61 months.

36. The method of claim 31, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and N-proBNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 7.5 months.

37. The method of claim 24 wherein said first marker is Big ET-1 (1-38) or its immunologically detectable fragments, and said cutoff level is about 2.4-5.0 fold the normal level and said second marker is BNP or its immunologically detectable fragments and said cutoff level is about 16-89 fold the normal level.

38. The method of claim 37, wherein said first marker is Big ET-1.

39. The method of claim 38, wherein said cutoff level of Big ET-1 (1-38) is about 3.5-5.0 fold the normal level for Big ET-1 (1-38).

40. The method of claim 38, wherein said cutoff level of Big ET-1 (1-38) is about 4.1 fold the normal level for Big ET-1 (1-38).

41. The method of claim 37, wherein said Big ET-1 or its immunologically detectable fragments is Big ET-1 (22-38).

42. The method of claim 41, wherein said cutoff level of Big ET-1 (22-38) is about 2.4-2.6 fold the normal level for Big ET-1 (22-38).

43. The method of claim 41, wherein said cutoff level of Big ET-1 (22-38) is about 2.5 fold the normal level for Big ET-1 (22-38).

44. The method of claim 37, wherein said cutoff level of BNP or its immunologically detectable fragments is about 32-89 fold the normal level for BNP or its immunologically detectable fragments.

45. The method of claim 37, wherein said cutoff level of BNP or its immunologically detectable fragments is about 54 fold the normal level for BNP or its immunologically detectable fragments.

46. The method of claim 37, wherein said cutoff level of BNP or its immunologically detectable fragments is about 16-21 fold the normal level for BNP or its immunologically detectable fragments.

47. The method of claim 37, wherein said cutoff level of BNP or its immunologically detectable fragments is about 18 fold the normal level for BNP or its immunologically detectable fragments.

48. The method of claim 37, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 31-44 months.

49. The method of claim 37, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 50% survival outcome from death by cardiovascular cause is about 4.5 months.

50. The method of claim 1 wherein said first marker is Big ET-1 (1-38) or its immunologically detectable fragments, and said cutoff level is about 2.4-5.0 fold the normal level and said second marker is ET-1 or its immunologically detectable fragments and said cutoff level is about 1.9-2.2 fold the normal level.

51. The method of claim 50, wherein said cutoff level of Big ET-1 (1-38) or its immunologically detectable fragments is about 3.5-5.0 fold the normal level for Big ET-1 (1-38) or its immunologically detectable fragments.

52. The method of claim 50, wherein said cutoff level of Big ET-1 (1-38) or its immunologically detectable fragments is about 4.1 fold the normal level for Big ET-1 (1-38) or its immunologically detectable fragments.

53. The method of claim 50, wherein said first marker is Big ET-1 (22-38).

54. The method of claim 52, wherein said cutoff level of Big ET-1 (22-38) is about 2.4-2.6 fold the normal level for Big ET-1 (22-38).

55. The method of claim 53, wherein said cutoff level of Big ET-1 (22-38) is about 2.5 fold the normal level for Big ET-1 (22-38).

56. The method of claim 50, wherein said cutoff level of ET-1 is about 2.1 fold the normal level for ET-1.

57. The method of claim 50, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and ET-1 or its immunologically detectable fragments are both below the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 37 months.

58. The method of claim 50, wherein when said level of Big ET-1 (1-38) or its immunologically detectable fragments and ET-1 or its immunologically detectable fragments are both more than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 4.5 months.

59. The method of claim 1 wherein said first marker is N-proBNP or its immunologically detectable fragments, and said cutoff level is about 4.7-6.8 fold the normal level and said second marker is BNP or its immunologically detectable fragments and said cutoff level is about 16-89 fold the normal level.

60. The method of claim 59, wherein said cutoff level of N-proBNP or its immunologically detectable fragments is about 5.7 fold the normal level for N-proBNP or its immunologically detectable fragments.

61. The method of claim 59, wherein said cutoff level of BNP or its immunologically detectable fragments is about 32-89 fold the normal level for BNP or its immunologically detectable fragments.

62. The method of claim 59, wherein said cutoff level of BNP or its immunologically detectable fragments is about 54 fold the normal level for BNP or its immunologically detectable fragments.

63. The method of claim 59, wherein said cutoff level of BNP or its immunologically detectable fragments is about 16-21 fold the normal level for BNP or its immunologically detectable fragments.

64. The method of claim 59, wherein said cutoff level of BNP or its immunologically detectable fragments is about 18 fold the normal level for BNP or its immunologically detectable fragments.

65. The method of claim 59, wherein when said level of N-ProBNP or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 50% survival outcome from death by cardiovascular cause is about 44 months.

66. The method of claim 59, wherein when said level of N-ProBNP or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 50% survival outcome for death by cardiovascular cause is about 5 months.

67. A method of predicting the survival outcome of an individual suffering from mild congestive heart cause, said method comprising:

a) determining as the first marker a level of proANP or its immunologically detectable fragments in the individual; and

b) determining as the second marker a level of proBNP or its immunologically detectable fragments or Big ET-1 (1-38) or its immunologically detectable fragments in the individual;

c) comparing the level of the first and second markers to cut-off levels of these markers in age matched normal individuals, said cut-off levels distinguishing between high and low survival rate,

wherein the likelihood of death from cardiovascular cause is greatest when said individual has first and second marker levels that are both greater than their cutoff levels, the likelihood of death from cardiovascular cause is least when said individual has first and second marker levels that are both less than their cutoff levels, and the likelihood of death

from cardiovascular cause is intermediate when said individual has one marker level greater than its cutoff level and the other marker level less than its cutoff level.

68. The method of claim 67, wherein said first marker is proANP.

69. The method of claim 67, wherein said first marker is N-proANP or its immunologically detectable fragments and said cutoff level is about 1.7-3.3 fold the normal level and said second marker is proBNP or its immunologically detectable fragments and said cutoff level is about 1.3-7 fold the normal level of proBNP or its immunologically detectable fragments.

70. The method of claim 69, wherein N-proANP or its immunologically detectable fragments is N-ProANP (1-98).

71. The method of claim 70, wherein said cutoff level of N-proANP (1-98) is about 1.7-2.2 fold the normal level for N-proANP (1-98).

72. The method of claim 70, wherein said cutoff level of N-proANP (1-98) is about 1.9 fold the normal level for N-proANP (1-98).

73. The method of claim 69, wherein N-proANP or its immunologically detectable fragments is N-ProANP (1-25).

74. The method of claim 73, wherein said cutoff level of N-proANP (1-25) is about 2.6-3.3 fold the normal level for N-proANP (1-25).

75. The method of claim 73, wherein said cutoff level of N-proANP (1-25) is about 3 fold the normal level for N-proANP (1-25).

76. The method of claim 69, wherein N-proANP or its immunologically detectable fragments is N-ProANP (68-98).

77. The method of claim 76, wherein said cutoff level of N-proANP (68-98) is about 2.4-3.1 fold the normal level for N-proANP (68-98).

78. The method of claim 76, wherein said cutoff level of N-proANP (68-98) is about 2.8 fold the normal level for N-proANP (68-98).

79. The method of claim 67, wherein said proBNP or its immunologically detectable fragments is BNP or its immunologically detectable fragments.



80. The method of claim 79, wherein said cutoff level of BNP or its immunologically detectable fragments is 2.6-7 fold the normal level for BNP or its immunologically detectable fragments.

81. The method of claim 79, wherein said cutoff level of BNP or its immunologically detectable fragments is 4.4-5.7 fold the normal level for BNP or its immunologically detectable fragments.

82. The method of claim 67, wherein said proBNP or its immunologically detectable fragments is N-proBNP or its immunologically detectable fragments.

83. The method of claim 82, wherein said cutoff level of N-proBNP or its immunologically detectable fragments is 1.3-1.8 fold the normal level for N-proBNP or its immunologically detectable fragments.

84. The method of claim 82, wherein said cutoff level of N-proBNP or its immunologically detectable fragments is 1.5 fold the normal level for N-proBNP or its immunologically detectable fragments.

85. The method of claim 67, wherein when said level of ProANP or its immunologically detectable fragments and proBNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is at least about 91 months.

86. The method of claim 67, wherein when said level of ProANP or its immunologically detectable fragments and proBNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is at about 35-42 months.

85. The method of claim 68, wherein when said level of N-ProANP or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both less than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is at least about 91 months.

86. The method of claim 68, wherein when said level of N-ProANP or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is about 35-42 months.

87. The method of claim 68, wherein when said level of N-ProANP or its immunologically detectable fragments and BNP or its immunologically detectable fragments are both more than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is about 40 months.

88. The method of claim 67, wherein mild congestive heart cause is defined as NYHA class I-II.

89. The method of claim 67, wherein said first marker is proANP or its immunologically detectable fragments and said cutoff level is about 1.7-3.3 fold the normal level and said second marker is Big ET-1 (1-38) or its immunologically detectable fragments and said cutoff level is about 1.6-2.4 fold the normal level.

90. The method of claim 89, wherein said first marker is proANP.

91. The method of claim 90, wherein said first marker is N-ProANP (1-98).

92. The method of claim 91, wherein said cutoff level of N-proANP (1-98) is about 1.7-2.2 fold the normal level for N-proANP (1-98).

93. The method of claim 91, wherein said cutoff level of N-proANP (1-98) is about 1.9 fold the normal level for N-proANP (1-98).

94. The method of claim 90, wherein said second marker is Big ET-1 (1-38).

95. The method of claim 94, wherein said cutoff level of Big ET-1 (1-38) is about 1.6-2.4 fold the normal level for Big ET-1 (1-38).

96. The method of claim 94, wherein said cutoff level of Big ET-1 (1-38) is about 2 fold the normal level for Big ET-1 (1-38).

97. The method of claim 90, wherein when said level of ProANP or its immunologically detectable fragments and Big ET-1 (1-38) or its immunologically detectable fragments are both less than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is at least about 90 months.

98. The method of claim 90, wherein when said level of ProANP or its immunologically detectable fragments and Big ET-1 (1-38) or its immunologically detectable fragments are both more than the cutoff level, the individual's 75% survival outcome for death by cardiovascular cause is about 40 months.